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(57) Abstract

The invention provides a method and composition for treatment of a nosocomial, microbial infection of a patient which comprises introduction into the gut of a patient an antimicrobial amount of an antimicrobial medicament which is cell wall constituent-inactivating, endotoxin non-releasing, exotoxin inactivating or a combination thereof. In particular, the invention provides the use of Taurolidine and/or Taurultam in the treatment of multi-resistant infections, e.g. VRE and MRSA.

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USE OF ANTIMICROBIAL AGENT SUCH AS TAUROLIDINE OR TAURULTAM IN THE MANUFACTURE OF A MEDICAMENT TO TREAT A NOSOCOMIAL MICROBIAL INFECTION

The present invention relates to the field of treating patients having microbial infections.

The broad use of antibiotics significantly influences multi-resistance of microorganisms, and has greatly increased the number of antibiotic-resistant microorganisms.

Antibiotic-resistant strains of Enterococci such as vancomycin-resistant strains of *Enterococcus faecium* and *Enterococcus faecalis* (VRE), as well as antibiotic-resistant strains of Staphylococci such as methicillin-resistant *Staphylococcus aureus* (MRSA) can cause severe nosocomial infections and diarrhea. Common nosocomial infections in intensive care units are pneumonia, urinary tract infections, septicemia, catheter-sepsis and postoperative wound infections.

Antibiotic-resistant microorganisms are increasingly associated with severe morbidity and mortality among hospitalized patients, particularly among patients with VRE colonizations in long-term care facilities and in those returning to community care, which now present a major public health threat. Management of life-threatening infections caused by antibiotic-resistant strains is particularly difficult, as the range of therapeutic options is very limited. There is a rapid increase in incidences of nosocomial infection and colonization with vancomycin-resistant Enterococci (VRE) throughout the whole world. Treatment options presently are combinations of antibiotics or experimental substances with uncertain efficacy. The potential emergence of vancomycin resistance in clinical isolates of *S. aureus* is dangerous. Successful prevention is necessary to prevent person-to-person transmission of VRE.

The compounds Taurolidine (Taurolin®) and Taurultam

are known antimicrobial substances with broad-spectrum activity against aerobic and anaerobic bacteria, mycobacteria and fungi. Unlike antibiotics, these compounds do not result in release of large quantities of bacterial toxins. They have been suggested as a substitute for antibiotics for administration in patients locally, by injection or by infusion, to combat infections of the teeth and jaw, wound infections, osteitis, endotoxaemia, peritonitis, sepsis and septic shock. However, it is known that these compounds have a short half-life *in vivo* and they never have been suggested for treatment of infections of the gut.

There remains an urgent need in the art for improved methods of treating patients with microbial antibiotic-multiresistant infections, including gut infections.

In one aspect the present invention provides the use of an antimicrobial medicament selected from the group consisting of antimicrobial medicaments which are cell wall constituent-inactivating, endotoxin non-releasing, exotoxin-inactivating, and combinations thereof, in the manufacture of a therapeutic agent, preferably an orally administrable therapeutic agent, for use in treating microbial infections of the digestive tract, intestinal tract or gut. Preferably, the medicament for use in the invention is a non-antibiotic medicament effective against antibiotic-resistant microbes.

In a further aspect the invention provides a method of treating a microbial infection of a patient which comprises introducing into the gut of the patient an antimicrobial amount of an antimicrobial medicament selected from the group consisting of antimicrobial medicaments which are cell wall constituent-inactivating, endotoxin non-releasing, exotoxin-inactivating, and combinations thereof, so as to treat the microbial gut infection of the patient. Preferably,

the medicament is orally administered.

As used herein, the term "patient" refers to a mammalian patient, preferably a human patient with microbial infection of the gut.

The antimicrobial compounds utilized in accordance with the invention are cell wall constituent-inactivating, endotoxin non-releasing, and/or exotoxin inactivating antimicrobial compounds, which are slow-acting bactericides. Preferably, the compounds are selected from the group consisting of non-antibiotic antimicrobial medicaments which are cell wall constituent-inactivating by cell wall cross-linking, non-antibiotic antimicrobial medicaments which are endotoxin non-releasing, non-antibiotic antimicrobial medicaments which are exotoxin-inactivating and combinations thereof. Particularly preferably, the compounds are cell wall-crosslinking compounds such as Taurolidine and Taurultam. Taurolidine is a unique antimicrobial agent having an exceptionally broad spectrum of antimicrobial and antibacterial activity including activity against gram positive and gram negative, aerobic, and anaerobic bacteria. Resistance has not been observed either *in vivo* or *in vitro*. Additionally, the compound possesses useful activity against most yeast-like and filamentous fungi.

The compounds Taurolidine and Taurultam are disclosed in US-A-5,210,083, the contents of which are incorporated herein by reference.

In a yet further aspect the invention thus provides a method of treating bacterial infection, fungal infection or a combination thereof in a patient, said method comprising orally administering so as to introduce into a patient's gut Taurolidine, Taurultam or a combination thereof, so as to treat said infection of said patient.

The antimicrobial compounds utilized in the present invention are distinguished from conventional

antibiotics as ordinarily understood in the art, i.e., antibiotics that act by attacking, breaking and/or rupturing microbial cell walls (disturbance of murein-biosynthesis, protein-biosynthesis, DNA topology, etc.), resulting in release of microbial toxins from the microbial cells.

While the invention is further described with respect to Taurolidine and Taurultam, the invention also is applicable to the use of other cell wall constituent-inactivating, antimicrobial compounds which release no or a substantially insignificant amount of toxins. Thus, the invention is applicable to Taurolidine, Taurultam, and antimicrobial medicaments which act in a substantially similar manner.

As indicated above, the present invention is directed to a method of treating a patient with microbial infection, such as bacterial infection, fungal infection or a combination thereof. In particular, the invention concerns treatment of bacterial and/or fungal gut infection. The method of the invention is particularly suitable for use in treating patients with bacterial colonizations, e.g. in treating infections associated with multi-resistant bacteria, such as MRSA and VRE.

In yet a further aspect, the invention provides a method of treating a microbial digestive tract infection of a patient, comprising introducing into the digestive tract of the patient a non-antibiotic, antimicrobial medicament effective against antibiotic-resistant microbes.

The invention is particularly applicable to microbial infections of the digestive tract, intestinal tract or gut, and is advantageous for use against infections of the gut by antibiotic-resistant microorganisms such as antibiotic-resistant strains of gram negative or gram positive bacteria, antibiotic-resistant and multi-resistant strains of Enterococci,

antibiotic-resistant and multi-resistant strains of Staphylococci, *Enterococcus faecalis*, *Enterococcus facium*, *Staphylococcus aureus*, vancomycin-resistant *Enterococcus faecalis* (VRE) strains, and methicillin-resistant *Staphylococcus aureus* (MRSA) strains.

The antimicrobial medicament can be administered as a tablet, capsule, liquid, suspension, suppository or the like, preferably as enteric coated tablets or capsules, ensuring biological availability, controlling the effects of the drug, and avoiding side effects.

In preferred embodiments, the antimicrobial medicament is administered enterally. One suitable method of administration is oral administration. For treatment of microbial infections of the lower bowel or colon, administration is preferably directly into the patient's gut, e.g. orally and/or rectally. In cases of severe microbial infection, bacteria may also be present in the blood stream. In such cases it may be desirable to administer the medicament both locally, e.g. by the oral and/or rectal route, and systemically, e.g. by means of a central catheter. Thus, further embodiments may include injection and/or intravenous administration of the antimicrobial medicament either alone, or in conjunction with oral and/or rectal administration.

In particularly preferred embodiments, the antimicrobial medicament is administered so that the medicament is substantially continuously present in the patient's gut over the course of the treatment, so as to inhibit microbial proliferation and/or reproduction in the patient's gut. Enteric coating of soft or hard gelatin capsules can be utilized to stabilize acid sensitivity, improve tolerance and avoid gastric lesions, gastric disorders, and irritation of the gastric mucosa after peroral administration. Enteric coating delays onset of action, and targets release in the small intestine.

The invention also is applicable to pharmaceutical

compositions for treatment of microbial infections. In a yet further aspect the invention thus provides a pharmaceutical composition comprising an antimicrobial medicament selected from the group consisting of antimicrobial medicaments which are cell wall constituent-inactivating, endotoxin non-releasing, exotoxin-inactivating, and combinations thereof, together with either a pharmaceutically acceptable delayed release excipient operatively associated with said medicament, or a pharmaceutically acceptable sustained release excipient operatively associated with said medicament.

Particularly preferred pharmaceutical compositions in accordance with the present invention, for treatment of microbial gut infections, include an antimicrobial amount of an antimicrobial medicament selected from the group consisting of antimicrobial medicaments which are cell wall constituent-inactivating, endotoxin non-releasing, exotoxin-inactivating, and combinations thereof, in a formulation selected from the group consisting of (1) delayed release formulations including a pharmaceutically acceptable delayed release excipient operatively associated with the antimicrobial medicament, which delays release of the medicament when administered orally until entry into a patient's intestinal tract, and (2) sustained release formulations including a pharmaceutically acceptable sustained release excipient operatively associated with the medicament so as to substantially continuously release the medicament after entry into a patient's intestinal tract. In particularly preferred sustained release formulations, the medicament is substantially continuously released after entry into a patient's intestinal tract for a period of at least one hour, more preferably at least 2, 3, 4, 5, 6, 7, 8 hours or longer.

Sustained and delayed release formulations can be made with:

1) Use of various matrices to control drug release, such matrices including various polymers (see e.g. US-A-5,618,559, US-A-5,637,320, US-A-5,648,096 and US-A-5,654,005), cellulosic materials (see e.g. US-A-5,607,695, US-A-5,609,884, US-A-5,624,683 and US-A-5,656,295) fatty acids and polyglycerols (see e.g. US-A-5,593,690, US-A-5,602,180 and US-A-5,628,993), polysaccharides (see e.g. US-A-5,629,018) and gelatin derivatives (see e.g. US-A-5,614,219).

2) Use of gastroresistant coatings including polymeric and vinylic coatings (see e.g. US-A-5,639,476, US-A-5,637,320, US-A-5,616,345, US-A-5,603,957, US-A-5,656,291, US-A-5,614,218, US-A-5,541,171 and US-A-5,541,170), and cellulosic coatings (see e.g. US-A-5,510,114 and US-A-5,603,957).

3) Use of additives to the active ingredients that prolong release, such as fatty acids (see e.g. US-A-5,597,562).

US-A-5,650,170 discloses dosage forms for delivering drugs at a controlled rate to the intestine and to the colon.

The contents of each of the above-cited U.S. Patents are incorporated herein by reference.

In preferred embodiments, the antimicrobial medicament is administered to the patient substantially continuously for a time period of about 5 to 10 days so as to substantially eliminate the microbial infection in the patient. Taurolin *in vitro* has proven to be effective against all gram negative and gram positive bacterial strains tested to-date, including antibiotic multi-resistant strains such as *Enterococcus faecalis* and *Enterococcus facium*, VRE and MRSA.

Enterococci are widely distributed in nature and mainly colonize the colon. Normally, Enterococci are not pathogenous. However, due to abuse of antibiotics such as vancomycin, as well as antibiotic additives in animal feed, multi-resistant bacterial strains can be

isolated as concurrent flora in infections of urinary passages, gall bladder infections and wound infections.

A most dangerous form of Enterococcus infection is endocarditis. Chronic diarrhea also is caused by such infection. VREs are especially dangerous as they can pass on their resistance to other bacterial strains such as *Staphylococcus aureus* or *Staphylococcus epidermidis*.

VREs can infect the gut and cause severe diarrhea. This can be treated in accordance with the present invention by oral administration of the antimicrobial medicament, but if sepsis is also present in the patient, concurrent intravenous administration of the antimicrobial medicament as a 2% sterile solution may be desirable.

MRSA, which can cause severe nosocomial infections, is particularly wide-spread with high incidences of fatality. In many cases, the patient must be isolated to prevent person-to-person transmission of the infection.

MRSA infection, in particular coagulase-negative Staphylococci infection, may be treatable by intravenous administration of the antimicrobial medicament alone, but if the patient is experiencing severe diarrhea, both oral and intravenous administration in combination may be desirable. MRSA can infect the skin and mucous membranes of patients, can be present in a patient's urine, and is easily transmitted to other persons. Additionally, MRSA-infected patients sometimes have meningitis.

Taurolidine and/or Taurultam may be administered in an aqueous solution at a concentration of about 0.1-3% (e.g. 0.5%) by weight Taurolidine and/or Taurultam. Suitable compositions are disclosed in US-A-5,210,083. Aqueous solutions of Taurolidine and/or Taurultam may be administered during the treatment period in a total amount of about 0.5-5 litres (which may correspond to 1 litre/2% per day, 20-30 g/24 hours/adult human patient

of Taurolidine).

Treatment of severe microbial gut infections in accordance with the present invention can save the lives of many patients, as compared to conventional treatments. Taurolidine and Taurultam destroy bacteria slowly, cross-linking the bacterial cell walls and thereby preventing the release of bacterial toxins. The cross-linking of the bacterial cell walls inactivates the bacterial toxins which could otherwise be highly poisonous. Additionally, because of this unique mode of action with bacterial cell walls, no resistance development by microbes has been observed.

Taurolidine and/or Taurultam prevent over-production of cytokines in the patient by monocytes of the blood which can arise as a result of infection. While addition of antibiotics to human blood leads to a rise in TNF-a, the addition of Taurolidine and/or Taurultam to antibiotic-treated cultures prevents a rise in TNF production as a result of nearly complete neutralization of released endotoxins.

While classic antibiotics act quickly, Taurolidine and/or Taurultam kill bacteria slowly. Furthermore the bacteraemia disappears slowly while treatment with Taurolidine and/or Taurultam continues over a period of time. Bacterial toxins are prevented from release, and no over-production of cytokines occurs.

The invention is illustrated by the following Examples, which are not intended to be limiting:

Example 1 (Capsules)

1. Soft-gelatin capsules, System Scherer®
Size 16 oblong
Content: 500 mg Taurolidine (crystalline)
Migliol™(medium chain triglyceride)
Softisan 367™ hard fat
600 mg (Caprylic, capric, stearic triglyceride)
Total filling weight 1100 mg.

2. Hard-gelatin capsules
Qualicap™ Lilly transparent/size 0
Contents: 300 mg Taurolidine (crystalline)
6 mg talc, Acrosil™, Mg-stearate 8:1:1 (additive)

306 mg

Example 2 (Tablets)

		Substance	Amount mg/Tablet
1		Taurolidine or Taurultam	300
		Emdex™ (Dextrates*) direct compression Dextrate	200
		Magnesium stearate	10
2		Taurolidine or Taurultam	300
		Methacell™ K4M premium (Hydroxypropyl methylcellulose)	200
		Corn Starch	12
		Magnesium stearate	10
		Gastric juice-resistant Endragit™ RS 100 and dibutylphthalate in methanol (7.2 parts and 0.8 parts)	

3.	Taurolidine or Taurultam	500
	Methocell™ E15LV premium	250
	Microcrystalline Cellulose	50
	Magnesium stearate	10
4.	Taurolidine or Taurultam	300
	Methocell™ E15LV premium (Hydroxypropylmethylcellulose)	200
	Microcrystalline Cellulose	50
	Talc	16
	Magnesium stearate	2
	Aerosil™ 200	2
	gastric juice-resistant Endragit™ (Polymethacrylate)	

*Dextrates, purified mixture of saccharides resulting from the controlled enzymatic hydrolysis of starch USP/HF 23/18

Dose: 3-4 tablets daily or more, and in severe cases, enough tablets or capsules to deliver to the patient up to 10 grams or more Taurolidine per day.

Example 3 - Taurolidine Minimum Inhibition Concentrations (MICs) for methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecalis* (VRE) strains.

Introduction

Methicillin-resistant *Staph. aureus* (EMRSA 15)

Because of their resistance characteristics, Staphylococci presently are the pathogens most responsible for severe nosocomial infections.

Against penicillinase resistant Betalactam-antibiotics such as methicillin, approximately 10% of

the Staphylococcus strains are resistant. Methicillin-resistance is very problematic in the clinic, as it often happens that a multi-resistance develops. It can initiate invasive and difficult to treat toxin-medicated infection processes. These Staphylococci are resistant against all antibiotics, including gyrase-inhibitors with the exception of vancomycin.

Vancomycin-resistant *Enterococcus faecalis*

In clinical practice, vancomycin-resistant strains of *Enterococcus faecalis* are on the increase.

Conclusion

Owing to its chemical mechanism of action with the bacterial cell wall, taurolidine is fully effective *in vitro* against pathogens which are resistant to antibiotics such as methicillin and vancomycin.

Taurolidine MICs for methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecalis* (VRE) strains.

Test strains

All test strains were clinical isolates recovered from patients attending Hammersmith Hospital, London. Strains of *Staphylococcus aureus* (epidemic methicillin-resistant strain 15 (EMRSA 15) and vancomycin-resistant *Enterococcus faecalis* were broadly unselected isolates from local culture collections. However, strain selection was conducted so as to ensure that isolates were not consecutive isolates from individual patients.

Local EMRSA 15 strains are typically resistant *in vitro* to penicillins, including methicillin (cloxacillin), erythromycin, clindamycin, ciprofloxacin, aminoglycosides and mupirocin. Commonly encountered strains of VRE, designated HAM-I, show high level gentamicin resistance in addition to resistance *in vitro*

to ampicillin, erythromycin, vancomycin, telcoplanin.

Disc Sensitivity testing

All routine sensitivity testing was performed using a standard disc diffusion technique (Stokes) performed on Unipath (Oxoid) Diagnostic Sensitivity Test agar with 5% lysed horse blood.

Control organisms

Testing of Staphylococci - *Staphylococcus aureus* (Oxford strain) NCTC 6571

Testing for Enterococci - *Enterococcus faecium* NCTC 12697

Inoculum & test procedure

Inocula for test and control organisms were prepared from overnight 37°C Unipath (Oxoid) Brain Heart Infusion broth cultures. From these well-mixed cultures, 2 drops (t/u ml) were transferred to 3 ml sterile water. This suspension was used to moisten sterile cotton tipped swabs which were then used with a rotary plater for inoculation of test plates.

Antibiotic discs

The following disc sets were used for sensitivity testing:

Staphylococci

Trimethoprim	5μg	Gentamicin	10μg
Benzyl penicillin	1 unit	Cloxacillin	5μg
Erythromycin	15μg	Rifampicin	2μg
Clindamicin	2μg	Teicoplanin	30μg
Fucidin	10μg	Ciprofloxacin	1μg
Vancomycin	30μg	Mupirocin	30μg

Enterococci

Ampicillin	10μg
Vancomycin	30μg
Teicoplanin	30μg
Gentamicin	200μg
Chloramphenicol	20μg
Erythromycin	15μg

Methicillin sensitivity testing

Methicillin (cloxacillin) sensitivity for Staphylococci was confirmed using a methicillin test strips (Methi-test, Medical Wire Limited - MW981) and a heavy inoculum. This was prepared by adding 5 colonies from an overnight nutrient agar plate culture 3ml water.

For each organism, including sensitive and resistant controls, a loop was charged with the heavy inoculum suspension and streaked across a Unipath (Oxoid) Diagnostic Sensitivity Test plus 5% lysed horse blood agar plate in a single direction. A methicillin strip was then placed on the surface of the plate at right angles to the inocula. Up to 4 test strains, plus sensitive (Oxford *Staphylococcus* NCTC 6571) and resistant controls were accommodated on each test plate. The plate was incubated overnight at 30°C.

Test interpretation

Methicillin

Test zones <5mm smaller than the control zone are SENSITIVE. Zones <5mm smaller than the control are RESISTANT. There is no indeterminate category with methicillin.

Other drugs

Except for methicillin tests, interpretation of results is based on the following criteria:

Sensitive	test zones greater than, equal to, or no more than 3mm smaller than the control zone
Resistant	test zones less than 3mm
Indeterminate	test zone greater than 3mm, but more than 3mm less than the control zone.

Taurolidine MICs

Taurolidine MICs were performed using a sample of authenticated anhydrous micronised taurolidine batch number E/40522/4 (Geistlich Pharma AG, Wolhusen, Switzerland).

An aqueous stock solution of taurolidine was prepared to contain 2g/100ml taurolidine in water. This preparation was solubilized and sterilized by heating to 121°C (15 psi) for 15 minutes.

Using this stock solution, serial doubling dilution of taurolidine were prepared in Unipath (Oxoid) Nutrient Broth Number 2 using 50μl volumes in sterile round bottom microdilution trays. To these dilutions was added an equal volume of drug-free broth containing a suspension of the test organism to give a final inoculum density of approximately 10^3 cfu. Inocula were prepared from overnight drug-free broth cultures of each test organism in Unipath (Oxoid) Nutrient Broth Number 2.

Final test concentrations of taurolidine were as follows:

2,000 mg/l	735 mg/l
1,500 mg/l	250 mg/l
1,000 mg/l	190 mg/l
750 mg/l	125 mg/l
500 mg/l	62 mg/l

All tests were incubated at 37°C for 18 hours. The MIC was defined as the lowest concentration of drug showing no visible evidence of growth.

Results

The results of disc sensitivity testing and taurolidine MICs are summarised below. There appears no difference in level of susceptibility to taurolidine for the strains examined when compared to the reference strain NCTC 6571 or the results from previous studies performed with fully sensitive strains.

	TRI	PEN	ERY	CLI	FUC	VAN	GEN	CLX	RIF	TEI	CIP	MUP	AMP	CHL	Taurolidine MIC (mg/fl)
S. aureus	S	R	R	R	S	S	R	R	S	S	R	R			500
	S	R	R	R	S	S	R	R	S	S	R	R			500
	S	R	R	R	S	S	R	R	S	S	R	R			500
	S	R	R	R	S	S	R	R	S	S	R	R			500
E. faecium			R			R	R			R			R	S	750
			R			R	R			R			R	S	375
			R			R	R			R			R	S	500
			R			R	R			R			R	S	375
S. aureus NCTI 6571	S	S	S	S	S	S	S	S	S	S	S	S	S	S	600

Example 4 - Taurolidine Susceptibility of Enterococcus Species

Worldwide, vancomycin-resistant strains of *Enterococcus faecium* and *Enterococcus faecalis* (VRE) are increasingly associated with severe morbidity and mortality among hospitalized patients. Particularly difficult is the increasing incidence of colonization with VRE seen among patients in long-term-care facilities and in those returning to community care which now present a major public health threat. Management of life-threatening infections caused by

these strains is particularly difficult as the range of therapeutic options is severely limited. Taurolidine (Taurolin®, Geistlich Pharma AG, Switzerland) is an antimicrobial medicament for parenteral or local administration and is characterized by broad spectrum of antimicrobial activity as well as potentially valuable cytokine-moderating (anti-endotoxic) activity.

The *in vitro* susceptibility to taurolidine of a panel of clinical isolates and reference strains of *Enterococcus faecium* (n=20,7 strains vancomycin resistant) and *Enterococcus faecalis* (n=53,5 strains vancomycin resistant) has been examined. There was no difference in degree of susceptibility between strains of *E. faecalis* (MIC mode 375 µg/ml, range 125-500 µg/ml) and *E. faecium* (MIC mode 375 µg/ml, range 95-375 µg/ml). In all cases, the Minimum Bacteriocidal Concentration (MBC) of taurolidine was within 2 dilutions of the corresponding value for MIC confirming a bactericidal mode of action. *In vitro* resistance to taurolidine was not observed.

No differences were noted between the MICs or MBCs for vancomycin-sensitive or vancomycin-resistant strains of Enterococci or for strains obtained from various locations across Europe (Switzerland, Germany, UK). On the basis of these limited *in vitro* data, taurolidine provides a further therapeutic option for selected patients with severe or life threatening infections caused by VRE. The activity of this agent against vancomycin-resistant and vancomycin-sensitive strains of Enterococci indicates that taurolidine adds a further dimension to the limited armamentarium available against these increasingly common bacterial pathogens.

The results are shown in Table 1.

TABLE 1

	E. faecium (all strains)		E. faecium (VAN R strains)		E. faecium (VAN S strains)	
	MIC	MBC	MIC	MBC	MIC	MBC
Mode	375	500	95	500	375	750
Avg.	260	581	161	446	323	666
Mean	260	581	161	446	323	666
Median	250	500	95	500	375	750
Min.	95	375	95	375	125	500
Max.	375	1000	250	500	375	1000

	E. faecalis (all strains)		E. faecalis (VAN R strains)		E. faecalis (VAN S strains)			E. faecalis (VAN S) model	
	MIC	MBC	MIC	MBC	MIC	MBC		MIC	MBC
Mode	375	500	250	500	250	500	UK	250	500
Avg.	310	606	213	500	289	566	Switzerland	375	500
Mean	310	606	213	500	289	566	Germany	375	750
Median	375	500	250	500	250	500			
Min.	125	375	125	500	190	375			
Max.	500	750	375	750	500	750			

Example 5

Two percent taurolidine solution was tested against various bacteria at $5x10^4$ CFU/well, according to Manual of Clinical Microbiology, 6th edition, P.R. Murray et al., pp. 1334-1335. The results are shown in Table 2.

TABLE 2

Sample No.	Organism	MIC(mg/lt) 24 h	MIC(mg/lt) 48 h	MBC(mg/lt) 24 h	VE[1] 30
1	E.faecium	190	250	500	S
2	E.faecium	375	375	500	S
3	E.faecium	190	250	500	S
4	E.faecium	250	250	375	R
5	E.faecium	250	250	375	R
6	E.faecium	</=95	190	50	R
7	E.faecium	125	375	500	S
8	E.faecium	</=95	190	500	R
9	E.faecium	</=95	250	500	R
10	E.faecium	190	375	750	S
11	Staph.app.	190	250	375	S
12	E.faecium	</=95	190	375	S
13	E.faecium	250	375	500	S
14	E.faecium	375	375	750	S
15	E.faecium	375	375	500	S
16	E.faecium	375	375	750	S
17	E.faecium	375	375	750	S
18	E.faecium	375	375	750	S
19	E.faecium	375	375	750	S
20	E.faecium	375	375	1000	S
21	E.faecalis	375	375	500	S
22	E.faecalis	250	375	500	S
23	E.faecalis	250	375	500	S
24	E.faecalis	375	375	500	S
25	E.faecalis	375	375	500	S
26	E.faecalis	375	375	500	S
27	E.faecalis	250	250	500	S

28	E.faecalis	250	375	500	S
29	E.faecalis	190	250	500	S
30	E.faecalis	190	250	500	S
31	E.faecalis	375	375	500	S
32	E.faecalis	375	375	500	S
33	E.faecalis	250	250	750	S
34	E.faecalis	250	375	500	S
35	E.faecalis	250	250	500	S
36	E.faecalis	250	375	500	R
37	E.faecalis	250	250	500	S
38	E.faecalis	250	375	500	R
39	E.faecalis	250	375	500	S
40	E.faecalis	250	375	500	S
41	E.faecalis	190	190	500	R
42	E.faecalis	125	190	500	R
43	E.faecalis	250	375	750	S
44	E.faecalis	250	375	500	R
45	E.faecalis	250	250	500	S
46	E.faecalis	250	250	500	S
47	E.faecalis	250	250	500	S
48	E.faecalis	375	375	500	S
49	E.faecalis	250	375	500	S
50	E.faecalis	375	375	500	S
51	E.faecalis	375	500	750	S
52	E.faecalis	190	375	750	S
53	E.faecalis	375	375	750	S
54	E.faecalis	500	500	750	S
55	E.faecalis	375	500	750	S
56	E.faecalis	250	375	375	S
57	E.faecalis	375	500	750	
58	E.faecalis	375	375	750	
59	E.faecalis	375	375	750	

60	E.faecalis	375	375	750	
61	E.faecalis	375	500	750	
62	E.faecalis	375	500	750	
63	E.faecalis	375	500	750	
64	E.faecalis	375	375	750	
65	E.faecalis	375	375	750	
66	E.faecalis	190	250	375	
67	E.faecalis	375	375	750	
68	E.faecalis	375	375	750	
69	E.faecalis	250	500	750	
70	E.faecalis	375	500	750	
71	E.faecalis	375	500	750	
72	E.faecalis	375	375	750	
73	E.faecalis	375	500	750	
74	E.faecalis	375	375	750	

[1]VE30: Resistance to Vancomycin (30 μg/Disc)

R = Resistant to Vancomycin (VE)

S = Sensitive to VE

Claims:

1. Use of an antimicrobial medicament selected from the group consisting of antimicrobial medicaments which are cell wall constituent-inactivating, endotoxin non-releasing, exotoxin-inactivating, and combinations thereof, in the manufacture of a therapeutic agent for use in treating microbial infections of the digestive tract, intestinal tract or gut.

2. Use as claimed in claim 1 wherein said medicament is a non-antibiotic medicament effective against antibiotic-resistant microbes.

3. Use as claimed in claim 1 or claim 2 wherein said therapeutic agent is administered in the form of a tablet, liquid, suspension or suppository.

4. Use as claimed in any one of claims 1 to 3 wherein said therapeutic agent is administered so that said medicament is continuously present in the gut over a course of the treatment.

5. Use as claimed in any one of claims 1 to 4 wherein said therapeutic agent is for use in oral and/or rectal administration of said medicament, optionally in conjunction with intravenous administration of said medicament.

6. Use as claimed in any preceding claim wherein the microbial infection is by an antibiotic-resistant microorganism.

7. Use as claimed in any preceding claim wherein the microbial infection is by a gram-negative or gram-positive bacterium.

8. Use as claimed in any one of claims 1 to 5 wherein the microbial infection is by Enterococci and/or Staphylococci.

9. Use as claimed in claim 8 wherein the microbial infection is by antibiotic-resistant Enterococci and/or Staphylococci.

10. Use as claimed in claim 9 wherein the Enterococci are vancomycin-resistant *Enterococcus faecalis* (VRE).

11. Use as claimed in claim 9 wherein the Staphylococci are methicillin-resistant *Staphylococcus aureus* (MRSA).

12. Use as claimed in any one of claims 1 to 5 wherein the microbial infection is by antibiotic-resistant *Enterococcus faecium*.

13. Use as claimed in any preceding claim wherein the antimicrobial medicament is selected from the group consisting of taurolidine, taurultam and a combination thereof.

14. A pharmaceutical composition comprising an antimicrobial medicament selected from the group consisting of antimicrobial medicaments which are cell wall constituent-inactivating, endotoxin non-releasing, exotoxin-inactivating, and combinations thereof, together with either a pharmaceutically acceptable delayed release excipient operatively associated with said medicament, or a pharmaceutically acceptable sustained release excipient operatively associated with said medicament.

15. A composition as claimed in claim 14 wherein said delayed release excipient is capable of delaying the release of said medicament when administered orally

until entry into a patient's intestinal tract.

16. A composition as claimed in claim 14 wherein said sustained release excipient is capable of substantially continuous release of said medicament after entry into a patient's intestinal tract for a period of at least about 3 hours, preferably for a period of at least about 8 hours.

17. A composition as claimed in any one of claims 14 to 16 for treatment of a microbial infection.

18. A method of treating a microbial infection in a patient, said method comprising introducing into the gut of said patient an antimicrobial amount of an antimicrobial medicament selected from the group consisting of antimicrobial medicaments which are cell wall constituent-inactivating, endotoxin non-releasing, exotoxin-inactivating, and combinations thereof, so as to treat said microbial infection of said patient.

19. A method of treating a microbial digestive tract infection of a patient, comprising introducing into the digestive tract of said patient a non-antibiotic, antimicrobial medicament effective against antibiotic-resistant microbes.

INTERNATIONAL SEARCH REPORT

Im ational Application No
PCT/GB 99/00028

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/54

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FOCHT ET AL: "spectrum of pathogens and resistance in peritonitis" LANGENBECKS ARCHIV FÜR CHIRURGIE, vol. 382, no. 4, 1997, pages s1-s4, XP002102968 see page S3 ---	1-13,18, 19
X	VANKEMMEL ET AL: "traitement anti-infectieux local et général par utilisation d'un nouvel antiseptique en chirurgie bilio-pancréatique: un défi aux antibiotiques" MED INTERNE, vol. 14, no. 12, 1979, pages 683-688, XP002102969 see the whole document --- -/--	1-4,6-9, 13,18,19

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 May 1999	01/06/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Trifilieff-Riolo, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int. ..tional Application No
PCT/GB 99/00028

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	RUEGSEGGER ET AL: "tauroline in intra-abdominal infections" HELV CHIR ACTA, vol. 45, no. 6, 1979, pages 743-747, XP002102970 see the whole document	1-4,6,8, 13,18,19
X	RIEGSEGGER ET AL: "comparative study on prophylactic antibiotics versus perioperative taurolidine in colonic surgery" HELVETICA CHIRUR ACTA, vol. 50, no. 1-2, 1983, pages 117-120, XP002102971 see the whole document	1-4,7, 13,18,19
X	ROSMAN ET AL: "effect of intraperitoneal antimicrobials on the concentration of bacteria, endotoxin and TNF in abdominal fluid and plasma in rats" EUR SURG RES, vol. 28, no. 5, 1996, pages 351-360, XP002102972 see page 358 - page 359	1-4,7, 13,18,19
X	GOERTZ G.: "local antiseptic and antiendotoxic measures in the case of intraabdominal infections" LANGENBECKS ARCHIV FÜR CHIRURGIE, vol. 382, no. 4, 1997, pages s37-s41, XP002102973 see abstract see page S39 - page S41	1-4,7, 13,18,19
X	LINDER ET AL: "therapy of purulent peritonitis" LANGENBECKS ARCH CHIR, vol. 353, no. 4, 1981, pages 241-250, XP002102974 see abstract	1-4,7, 13,18,19
X	BROWNE M.K.: "the treatment of peritonitis by an antiseptic taurolin" PHARMATHERAPEUTICA, vol. 2, no. 8, 1981, pages 517-522, XP002102975 see the whole document	1-4,7, 13,18,19
X	WO 90 06138 A (HOLMES MICHAEL JOHN ;GEISTLICH SOEHNE AG (CH)) 14 June 1990 see page 6; examples 1-5	14-17

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/00028

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 18 and 19
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 18 and 19 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
In view of the large number of compounds which are defined by the wording of the claims, the search has been performed on the general idea and compounds mentioned in the examples of the description.

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte ional Application No
PCT/GB 99/00028

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9006138 A	14-06-1990	CA 2004166 A	31-05-1990
		DE 68913991 D	21-04-1994
		DE 68913991 T	14-07-1994
		EP 0446262 A	18-09-1991
		ES 2063333 T	01-01-1995
		JP 2873082 B	24-03-1999
		JP 4502414 T	07-05-1992
		US 5819748 A	13-10-1998